Appendix 2

The Frail Proof FAQ

1/7/25

Frequently Asked Questions about Hormone Therapies

These are the questions most frequently posted on social media with most of the answers digested from the book, which in turn was derived from the peer-reviewed research, popular books on menopause, and the answers posted to those questions on social media (which are collectively commonly referred to as being the "broscience"). It is the standard FAQ for the FaceBook group "**Menopausal Hormone Therapies**": If you don't find the answer to your question here, please ask in that group. Please download and refer to the book and the links on https://www.frailproof.com/ for more information and supporting references.

This list and the Frail Proof protocol in general is oriented toward US audiences. The hormones, lab tests, and protocols in other countries will vary somewhat although the underlying conditions and general solutions are the same. Prices shown are in USD.

In these questions and on social media in general, the following abbreviations are used:

T = testosterone
DHT = Dihydrotestosterone (most masculinizing form of T)
E = estrogen (all forms)
E1 = estrone, the "old woman" estrogen, produced by fat
E2 = estradiol, the most potent form, produced by the ovaries
E3 = estriol, the weakest form, doesn't protect bones/brain/skin
FSH = Follicle-stimulating hormone, a measure of Free E2
P = progesterone (also progestins and progestogens in general)
OMP = oral micronized progesterone (generic Prometrium, a P)
OHPC = hydroxyprogesterone caproate (generic Makena, a P)
MPA = medroxyprogesterone acetate (generic Provera, a P)
NETA = norethindrone acetate (generic Aygestin, a P)
GP = general practitioner (a family doctor)
PCP = primary care physician (same as GP)
NP = nurse practitioner (lowest certification to prescribe)
PA = physician's assistant (between NP and MD)
WP = Wiley protocol, a high-dose cyclic transdermal protocol
SS = Suzanne Somers a major proponent of WP-like protocols

SHBG = sex hormone binding globulin, disables T and E2
Free (X) = Hormone (E2 or T) not bound by SHBG
TSH = thyroid stimulating hormone
FT3, RT3 = Free T3 and Reverse T3
DIM = Diindolylmethane, a supplement to reduce "bad" estrogens
surmeno = Surgical menopause (having ovaries removed)

Units are most commonly omitted when quoting levels because most US labs, and most notably both Quest and Labcorp, use the same units. Different labs do have different ranges, however, and you need those ranges to make the call about whether a level is high or low. To convert US units to European units (usually in nmol rather than pg or ng) divide by (roughly) 3. More precise conversion calculators can be found on-line.

1) Do I need hormone therapy? How will I benefit?

Every one of the current generation of books on menopause recommends it for postmenopausal women, although the specific protocol recommendations vary considerably (see http://www.frailproof.com/FPBG.pdf for the details). A more complete consensus is seldom seen in the medical field. For men the answer is more qualified: If you have any of the symptoms of low testosterone (weight gain, loss of strength or muscle mass, mood or motivational disorders, sexual dysfunction, and many others) and test low on Free T, you will almost certainly benefit.

And the benefits are primarily in quality of life, not just quantity. Beyond mere alleviation of the symptoms of menopause and andropause, hormone therapies simply make you look, feel, and act younger, slowing or in many cases even reversing the aging process.

2) Is hormone therapy safe?

It is definitely safer than doing without: Even in the most negative (albeit very poorly done) study of hormone therapies, the Women's Health Initiative, all-causes death was lower in the treatment group than for the women who did not receive hormones, albeit with increases in some specific conditions (blood clots and breast cancer in particular). And that data was collected more than 20 years ago: With more modern protocols, especially those that don't rely on fully-synthetic oral hormones like Premarin and MPA, risk is lower even for those conditions.

3) *When should I start hormone therapy?*

Women should start P therapy as soon as symptoms like hot flashes first appear or periods start to become irregular (perimenopause), cyclically/sequentially (days 14-25 each cycle) at first, and then continuously (same dose every day) as perimenopause progresses to full menopause (which is best assessed using the AMH blood test). Because P declines first, women typically become estrogen dominant for up to a few years, leading to a greatly increased risk of endometrial proliferation/hyperplasia which can cause blood spotting and breakthrough bleeding. This in turn is associated with a significant increase in the risk of cancer but more importantly of getting talked into having a hysterectomy when all they really need is P supplementation.

E2 and T decline more slowly: By the time menopause starts they have dropped by roughly half and can take years to drop down to postmenopausal (negligible) levels. Therefore E2 and T therapy can be started immediately with P, but with proportionately smaller doses: It is possible to go through menopause experiencing none of the side effects women typically report and to fully protect bone and muscle mass during the transition.

4) *Can I start after age X?*

There are no specific age restrictions on hormone therapies, neither for men nor women. Although there is relatively little data on women starting or continuing therapies after age 60, the data from studies on men even much older than that (even into their 90s) is encouraging: They gain strength, muscle mass, mental clarity, and "grit" and with a very low incidence of side effects and a *decrease* in risk of cancer and heart disease.

There's also no need to ever stop hormone therapies: The 10-year window old-school docs use is an archaic concept not supported by more modern research.

5) *Will hormone therapy cause weight gain?*

While supplementing E, P, and/or T can cause some water retention, and hence some weight gain, none of them should cause fat accumulation, and E2 and T supplementation will generally reduce existing fat mass. T when combined with weight-bearing

exercise will generally result in increased muscle mass, again increasing weight but not fat. The one exception to this rule is that E2 and T both interact with thyroid hormones, causing or exacerbating hypothyroidism. A full thyroid panel should be done prior to starting HRT/TRT and retesting and thyroid hormone dosing adjusted within a few months of reaching a stable protocol. It's difficult to impossible to lose or even maintain a stable weight if you are hypothyroid.

6) *My doctor wants to prescribe X, which I don't want, or won't prescribe Y, which I do. What can I do?*

Change doctors. The "standard of care" in HT/HRT/TRT and for thyroid issues and diabetes is at least a decade behind the peer-reviewed science, and many doctors are even more backward than that. The odds of receiving appropriate hormone therapy from a General Practitioner (GP) are close enough to zero as to rule out even considering this. Odds are only slightly better with urologists, gynecologists, and endocrinologists who are not much more likely to even be aware of the state of the art in this field let alone be providing treatment at that level.

So, in most cases you'll need to find a "functional", "integrative", or "anti-aging" specialist or a clinic that specializes in hormone therapies. A good place to start is The American Academy of Anti-Aging Medicine (A4M) doctor locator: https://www.a4m.com/find-a-doctor.html, keeping in mind that many of these doctors will support clients without ever even seeing them ("concierge telemedicine"), using local providers for the physical exams. Or do an Internet search for those terms specifying your city or state/province. But even after you find a candidate, gather as much information about the therapies they prescribe before signing up for a consultation to ensure that they're a good fit and that you're not just wasting each other's time.

7) *Can I get insurance to pay for these therapies?*

In general, no. Most insurance plans, specifically including Medicaid and Medicare, do not cover state of the art treatments (including prescribing hCG for men and testosterone for women), in part because they are not FDA approved (i.e., modern hormone therapy relies heavily on off-label uses of hormones and other drugs). Trying to mix and match (trying to get a GP to order some of the tests and hormones that may be covered by insurance while

having a specialist order the rest) generally only results in frustrating both doctors and yourself.

8) *How much will this cost?*

The cost varies a lot depending on the protocol you and your doctor choose. It also will cost two or three times as much the first year, while you are tweaking your protocol, as in subsequent years. The going rate for start-up consultations ranges from $250 to $500, with less expensive follow up consultations being required a few times a year to start and as little once a year ongoing. Blood tests generally run about $250 per batch and must be done several times the first year, but probably only once or twice a year once you get your protocol down. If your doctor quotes significantly more than that for labs, order them yourself through one of the various on-line lab companies (e.g., https://www.ultalabtests.com/thyroidpharmacist/).

For the hormones, generic compounded creams and patches (transdermal application) and synthetic oral products are generally the least expensive, figure $200 to $400 a year. Injections generally run $300-$500 a year depending on whether you can use factory-produced compounds (e.g., Depo-Testosterone and Depo-Provera) or need compounded products (OHPC is only available compounded and many people have reactions to the carrier oils in factory-produced products). Note that at least some injections are required for men since hCG is only available by injection. Brand-name creams, such as for the Wiley Protocol (WP), generally run 2 to 3 times that much (up to $1000/yr). Pellets can be that much or more because they require minor surgery to insert, a procedure that must be repeated about 4 times a year, and because P can't be pelletized in endometrium-protective quantities you have to add in the cost of some other form of that. For both WP and pellets the cost will be more for women than men whereas for injection the costs will be similar (the cost of the hormones themselves and the total quantities injected are similar).

9) *Is T required for women?*

Although few of the current crop of menopause books specifically recommend this, the peer-reviewed literature and broscience are unequivocal: Insufficient T is nearly universal in postmenopausal women and supplemental T provides a great many benefits to them. It may not be necessary if mere symptom relief is the goal,

but is an essential component of any optimization protocol where the goal is to preserve the muscle mass, mood, libido, and "grit" that are characteristic of younger adults.

10) My T is X, is that good?

It is essentially useless to test or quote total testosterone levels because the effective (available for your body to use) amounts depend on SHBG levels which vary tremendously between individuals and even over time depending on what treatments you are receiving. You really only need to know "Free T" and so should only test and quote that. The "good" levels, for both men and women, are around the top of the lab range (4 to 5 for women for LabCorp, Quest results are currently far less predictable and so may not be useful for monitoring HRT). This provides maximum benefits with minimal risk of side effects. Note that this rule also applies to quoting E2 levels if you're not supplementing T: SHBG preferentially binds T, but if Free T is too low it will bind up more E2 making your symptoms correspond with a much lower value than your labs would indicate.

11) What are the best target levels for E2 and P? What doses will achieve these?

For symptom relief it is usually sufficient to raise E2 to 20 to 40 for both men and women. For women seeking to optimize levels to premenopausal levels to achieve maximum benefits in skin, hair, bones, heart, and libido, a target near the median level in premenopausal women is frequently used, around 100, or even better to use FSH to inform dosing (optimal being 5, the median level in premenopausal women). Some cyclic protocols target much higher levels (in the hundreds), but only for part of the month after which a period will clear out any accumulated endometrial tissue.

According to the peer-reviewed research, P levels for women on continuous protocols must be at least 5 to provide endometrial protection, a level that drastically reduces the risk of uterine cancer. Most practitioners furthermore try to balance E2 with P, specifying ratios of 50:1 to 100:1 (accounting for the difference in units, a factor of 1000). So a P of 5 would correspond to an E2 of 100. For cyclic protocols, P needs to be raised high enough to trigger a premenopausal-quality period.

As for dosing, tor injections starting T-cyp doses for women are roughly 15mg/wk, dosed once or twice a week. For E-cyp and E-val, 1.5mg/wk is a reasonable starting dose. For bioidentical P, 20mg/day, for OHPC about 120mg/wk.

For transdermal note that these recommendations refer to the hormones themselves, not the volume or weight of the cream: If all you have is the volume, multiply the dose size in ml by the cream concentration in mg/ml to convert to mg. Note that You must ***always*** dose transdermal hormones twice a day: Half life of those is too short for anything less. Starting doses for T are 5mg/day. Starting E2 dose is 3mg/day, and for P 80mg/day is a minimum safe dose. Note that many doctors prescribe less P than this, but the peer reviewed research is unequivocal on this: Doses less than 80mg/day simply do not provide sufficient endometrial protection vastly increasing the risk of spotting, bleeding, cancer, and hysterectomy.

Minimum safe OMP dose is 200mg day, split breakfast and dinner. Again, most docs underdose OMP in an attempt to minimize side effects and say to take it before bed. Again, the peer-reviewed research is unequivocal on this: It is simply unsafe to take OMP on an empty stomach or only once a day unless the dose size is vastly increased because absorption is so poor and the half-life is too short. Also note that you must order the LCMS version of the P lab test when using OMP: The standard test significantly overestimates level of protection because it reacts to P metabolites that do not provide endometrial protection. If you do not tolerate OMP orally (grogginess being the most common side effect), especially when taken during the day, use it TV or TR, where it may be sufficient to take it once a day (see prescribing information for Crinone). Another good option is to use 100mg TV/TR in the morning and 100 (or more) oral in the evening.

It is not safe to take T orally or as a troche: Most of it simply gets digested, but metabolites generated may be hepatotoxic (kills liver cells). It is not safe to take E2 orally because the majority of it metabolizes into E1 which increases the risk of breast and ovarian cancer. It also significantly increases the risk of blood clots.

Redo labs a month after every significant protocol change and adjust dosing as necessary to achieve target levels.

12) My TSH is X, is that good?

TSH is essentially useless as a means of diagnosing or monitoring treatment of thyroid issues (review the information on https://stopthethyroidmadness.com/ for why). Which of course will be news to most doctors because their standard of care is, again, decades behind the state of the art. TSH level is a very indirect measurement of thyroid function since TSH only stimulates the thyroid to produce T4 which then gets metabolized into T3, the active form of the hormone. And even most of that is bound up and so not active.

So you only need to test Free T3 and then adjust dosing to get it to around 3.5, roughly the 66th percentile of the lab range. Lower than that and you'll most likely experience symptoms of hypothyroidism, higher than that of hyperthyroidism. If T3 is low and you require treatment you should overwhelmingly prefer DTE/NDT (desiccated thyroid extract/natural dehydrated thyroid) such as Armour or Nature-throid over T4-only drugs (Synthroid). If your doctor won't prescribe one of them, see question #4 or at least insist on testing Reverse T3 (RT3), the inhibitory form of the active thyroid hormone: If it is elevated (above the middle of the lab range) no amount of T4 will alleviate your symptoms and it may even make them worse because your body will just convert more of it to RT3 than to Free T3.

TSH under appropriate treatment will generally drop below the bottom of the lab range (0.4) but optimally should remain at or above 0.1. Note that most docs will attempt to reduce dosage to keep TSH above the lab range minimum of 0.4: If they do this, recognize that they are using obsolete information (e.g., some will try to convince you that it puts you at risk of osteoporosis which was shown many years ago to be a misconception so long as FT3 dose not go above 3.5) and again see question #4. Testing for thyroid antibodies (TPO and Thyroglobulin) to diagnose Hashimoto's is not strictly necessary as the treatment is the same regardless of whether you have it or not: The primary reason for including them is to help convince your doctor that treatment is necessary even though low Free T3 or high Reverse T3 should be sufficient to do so.

13) What's the best hormone protocol, oral, creams, patches, injections, suppositories, or pellets?

Make no mistake: Any treatment, even the "standard of care" low dose oral Prempro (equine estrogens with MPA), is safer and better than no treatment at all. Whether you can upgrade from that depends primarily on whether you can find and afford to pay for a progressive doctor.

There is much debate and yet no consensus on which protocol is best, neither on social media nor in the peer-reviewed research nor in the many books that have been published on menopause and hormone therapies. To some extent it depends on individual metabolism, motivation, available time and financial resources, tolerance for side effects (primarily associated with oral and pellets, pellets due primarily to the very common issues with dose regulation) and pain tolerance and squeamishness (associated with injections and pellets). Choosing a particular protocol yourself does obligate you to do the research necessary to compare all of the options, so one obvious answer is to choose a good doctor first and let them help you choose the protocol.

That said, injections have the reputation of being the "elite" protocol because they impose the greatest technical burden on the client but also offer by far the best control over dosing and the associated increase in safety and effectiveness and with the smallest incidence of side effects. They're also significantly cheaper than pellets or name-brand transdermal (roughly 1/3 the cost). For men, the decision is easier: hCG can only be supplied by injection and most elite practitioners consider this an essential component of an optimization protocol. For women OHPC occupies a similar position. As long as you're doing one injection it only makes sense to get all your hormones that way. Second best would have to be transdermal/transvaginal/transrectal: Good level control and reasonable pricing, but with significantly more trouble (P must be dosed twice a day, the other hormones at least once a day). Pellets are a distant third: Expensive, poor level control, and a (relatively) high failure rate. Oral is fourth: Only acceptable if you can't get anything else.

14) Should I use "bioidentical" hormones, or are synthetics OK?

After an enormous amount of debate on this issue there is no clear picture other than that mode is vastly more important than the

substance. For example 90% of oral micronized progesterone (ostensibly bioidentical) is metabolized by the liver and digestive system into roughly 30 different chemicals, many of which are not found in significant levels in untreated women, and many of which cause serious side effects (anxiety and sleepiness being two of the most common). This problem with "first pass" metabolism affects most other compounds when delivered orally, regardless of whether they started out as bioidentical or fully synthetic.

Any remaining differences between synthetic and bioidentical hormones are small by comparison, so it's generally better to choose them based on dosing reliability, frequency of side effects, or cost than being a stickler for detail on how they are produced. If oral micronized progesterone makes you groggy, troches or wafers for sublingual or transbuccal administration (dissolving under the tongue or between the cheek and gum) taste terrible to you, and/or you find the twice-a-day application of creams too burdensome, or if any of the above don't reliably keep your serum P level above 5, consider substituting an oral synthetic (even MPA) or OHPC injections which don't have any of these issues. All are safer overall than reducing the dose size of the bioidentical in an attempt to mitigate side effects.

One "bioidentical" to avoid is estriol (E3), and pills or creams that contain it (Biest or Triest, which contain E3 with some E2 and sometimes E1). Estriol is an extremely weak form of estrogen (30 to 100 times weaker than estradiol) and while it can help some with symptom relief it does not offer the same protection to bones/hair/skin as estradiol and so is not suitable as a component of an optimization protocol. Regardless of whether E3 is included in a protocol or not, E2 levels must be still optimized by dosing appropriately.

15) Are cyclic/sequential protocols better than continuous protocols?

There is also considerable disagreement on this issue in both the broscience and menopause books. The peer-reviewed research is much clearer, however: Continuous protocols have been shown to cut the risk of endometrial cancer by up to 50% over cyclic protocols such as the Wiley Protocol. The issue here is whether the dosing of P causes a sufficiently robust flushing and/or resorption of the endometrial tissue that grows during the low-P portion of the cycle. If it does not, the risk of endometrial cancer skyrockets

in proportion to the amount of endometrial tissue: A stripe over 11mm thick is hundreds of times more likely to result in cancer than a stripe 5mm or less (for frame of reference this difference in risk is many times greater than that of smoking, drinking, high blood pressure, high cholesterol, and diabetes *combined*).

A fundamental misconception apparent in the proponents of cyclic protocols is that they're somehow more "natural" because they attempt to continue the monthly menstrual cycle in postmenopausal women. In fact, humans evolved in an environment where periods were very rare because women were either pregnant or nursing (both of which suppress menstruation) almost continuously. Looking at it from this perspective menstruation must be perceived as an "emergency eject" feature to be activated only in the relatively rare case where an egg released during ovulation did not get fertilized. The "natural" state of women is therefore much more similar to what is achieved with continuous protocols: Relatively high levels that slowly increase over 9 months of pregnancy followed by lower and more stable levels for approximately 3 years during nursing (E2 levels during nursing are in the same ballpark as the median level over the menstrual cycle albeit somewhat lower for some women). The second justification is that cyclic protocols somehow preserve or renew receptor sensitivity, a claim for which there is exactly zero support in the peer-reviewed research. This sort of "habituation" or "tolerance effect" has never been reported in the TRT literature either.

16) I have blood spotting, should I be worried?

The short answer is "yes", but only a little: The greatest risk associated with blood spotting is not cancer, it's a doctor ordering an unnecessary hysterectomy: 600,000 of these procedures are performed in the US alone, at least 90% of which are unnecessary. There is a significant risk of cancer too, however, which is why the better-safe-than-sued doctors frequently try to take the easy way out rather than investing the time to figure out what's going wrong with your levels and/or protocol and fixing that.

Approximately 75% of cases of bleeding in postmenopausal women are caused by endometrial atrophy, where the endometrial lining is too thin (less than 4mm) due to a lack of estrogen and so is easily damaged. The second most common cause is endometrial proliferation/hyperplasia, where too much estrogen is available in

relation to the level of a P that would check this growth. Although this tissue growth is caused by estrogen, the real problem is usually that the P level is not sufficient to suppress it. In both of these cases reducing E (unfortunately the approach most often chosen by doctors) is generally the exactly the wrong thing to do. Instead P must be increased, or possibly both P and E2 increased, either by increasing the dosage or changing the form, mode, or frequency of application. For example, transdermal P must be applied twice a day because dosing only once a day can cause a premature period: It is the drop in P level that causes a period and even the drop in level over 24 hours can be enough to do this. Note that this issue is particularly important to follow up on with continuous protocols or cyclic protocols that are not causing a premenopausal-quantity period each month, a robust period being a backstop that addresses the issue within a month of when the growth occurs.

Bleeding is also a sign that proper testing is not being done: A failure on the doctor's part, and a clear signal that it's time to shop for a new doctor. In addition to monitoring serum levels (or doing the dosing math correctly for synthetics) to ensure that a proper P to E ratio is being maintained, a uterine ultrasound should be ordered within 6 months of establishing a settled protocol. This simple, painless, and reasonably priced test (should be around $250) provides great peace of mind because of the vast increase in risk of cancer associated with a thick endometrium (greater than 6mm), especially when there is also blood spotting.

Whatever else you do, do *not* adjust your P dosage in an attempt to minimize side effects or use those side effects to your advantage (e.g., many women inappropriately use OMP as a sort of sleeping pill, varying their dose based on how much sleep they need, grogginess being one of the most common side effects of OMP). This is a sure-fire way to end up with one of those unnecessary hysterectomies because it results in chronic underdosing.

17) Is there an injectable P?

Yes, but due to its short half-life (less than 24 hours) natural progesterone would have to be injected at least every day, with twice a day being preferred. And those shots can be very painful because the compound is an irritant at high concentrations. Fortunately there are two alternatives, MPA and OHPC.

Injectable MPA (Depo-Provera) has been used as a long-acting contraceptive since the 1980s. It's safe and effective and with fewer side effects than are associated with oral MPA (e.g., as the progestin component of Prempro). Even better is OHPC (hydroxyprogesterone caproate, generic Makena) the synthetic most similar to natural progesterone in structure and effect. In the US it is used primarily for pregnancy support, but it is used by millions of women in China as the P component of a once-a-month injectable contraceptive.

OHPC only needs to be injected once or twice a week, MPA only about once a month. SC/SQ (just under the skin) injections of these compounds are more effective and far less painful than old-school IM (deep into the muscle) injections.

18) Which is better, blood (serum) or saliva testing?

Although a few of the current crop of menopause books recommend saliva testing, most don't and the peer-reviewed research is unequivocal: All recent published research uses serum testing, and the review/survey articles that discuss saliva testing universally report that it is not reliable enough to be used for diagnosis or treatment of any condition. Serum testing much more closely reflects the availability of hormones to all of the tissues of the body, not just the lymphatic system that is more selectively involved in transdermal application and saliva or blood spot testing. Urine testing can also be accurate, but is more expensive than serum testing and many levels can't be measured that way.

19) I have symptom X, will supplement Y fix this?

In general, no, unless you're exceptionally susceptible to the placebo effect. While certain nutritional supplements (vitamins and minerals) can have very limited benefits in addressing overt deficiencies (see the section on supplements in **Frail Proof** for the details), herbal supplements in general have no place in an anti-aging or hormone optimization protocol. This is one area where the FDA and the medical profession have it right and their position is backed up by even the latest peer-reviewed research: Herbal supplements are at best ineffective (indeed, independent testing has shown that many of them contain little or none of the compound they're supposed to be providing!) and in most cases interfere with proper treatment, cause debilitating side effects, or even are directly harmful. Be especially skeptical if your doctor is

selling the supplements they are recommending. If you're still inclined to try one be sure to first read the reviews of that supplement on sites such as https://labdoor.com/ and https://www.drugs.com/.